IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	(	Art Unit: 1615
Katsuya MATSUDA et al	(	Examiner: P. KULKOSKY
Appln. No.: 09/807,190	(	Confirmation No. 4190
Filed: April 10, 2000	(	Washington D.C.
For: POLYMER PARTICLES COMBINING WITH PHOSPHORIC ACID AND PREPARATION CONTAINING THE SAME	(	November, 2003

DECLARATION UNDER CFR 1.132

Honorable Commissioner for Patents and Trademarks,

Washington, D.C. 20231

Sir:

I, Katsuya MATSUDA, declare and state that I am one of the applicants of the above-identified patent application.

I declare that I graduated in March 1981 from the Faculty of Technology, Keio University, Yokohama, Japan and that I received a bachelor degree in Engineering from the same University.

I declare further that I have been employed by Chugai Seiyaku Kabushiki Kaisha, the assignee of the present application, since 1981 and that I have been engaged, as a researcher, in research into solid dosage formulations.

I declare further that I am a Senior Researcher at

Production Technology Laboratory of the Assignee.

I declare further that I have read all of the Official Actions in the above-identified application, and have read and am familiar with each of the references cited in the Official Action by the Examiner.

I declare further that the following test was conducted at my direction or under my supervision, and that the test results are true and correct to the best of my knowledge.

1. The relation between the method for preparation of phosphate-binding polymer particles and the true specific gravity of the polymer particles:

According to the method described in "Preparation 1" or "Preparation 2" on page 12 of the specification of the present application, phosphate-binding polymer particles were prepared by crosslinking polyallylamine with epichlorohydrin in a mixed medium of water/acetonitrile (ca. 50:50 w/w) (Preparation 1) or in water (Preparation 2).

The conditions for conducting the method for preparation of phosphate-binding polymer particles (Lots (a), (d) and (i) are summarized in Table I below.

Table I

Lot	a	d	i
Production Scale	30.9(kg)	63(kg)	59.7(kg)
Polyallylamine	1	1	1
Water	4	4	4
Sodium hydroxide	0.28	0.3	0.306
Acetonitrile	0	4.8	4.8
Epichlorohydrin	0.093	0.094	0.094

The resulting polymer was dried and ground into particles of water-containing phosphate-binding polymer particles and the true specific gravity of the polymer particles was measured using an apparatus for measuring true specific gravity (Acupick Model 1330, Shimazu Seisakusho K. K. Japan) by means of Helium gas substitution method.

The results are shown in the following Table Ⅱ.

Table Ⅱ

Solvent Used	Lot	True Specific Gravity(g/ml)	Remarks
Water	a*	1.2530	* The data shown in Table 1 on page 13 of the present application. (Samples prepared by the method of Holmes)
	b*	1.2527	
	c	1.2549	
Water/Acetonitril	d**	1.2094	**The data shown in Table 1 on page 13 of the present application
	e**	1.2107	
	f**	1.2108	
	g	1.2062	
	h	1.2174	
	i	1.2084	
	j	1.2049	
	k	1.2044	
	l	1.2087	
	m	1.2089	

In Table II, Lots (a)-(c) were prepared by "A" company with use of water as solvent used; Lots (d)-(h) were prepared by "A" company with use of a mixture of water and acetoritrile as solvent used; and Lots (i)-(m) were prepared by "D" company with use of a mixture of water and acetonitirile as solvent used. The detailed process for preparation of each of Lots (a), (d) and (i) as representative Lots is illustrated as follows:

[Lot (a)]

To a reaction kettle, were added a 50% poly(allylamine hydrochloride) aqueous solution (75.2 kg), which corresponds to 37.6 kg of poly(allylamine hydrochloride), and water (112 kg). The mixture was stirred and the pH was adjusted to 10 with NaOH. While stirring the solution, epichlorohydrin (3.5 kg) was added and the mixture was stirred until it gelled. The resulting gel was allowed to continued curing for 18 hours at room temperature, and then removed and ground in a grinder (500 rpm, 0.125 inch-screen). The gel was put in a filtration system and water was added to the system to allow the gel to be swollen. Water was removed by filtration to rinse the gel. The rinsing was repeated until the electric conductivity of the filtrate reached at less than 1.0 mS/cm. Then, the gel was dried in a dryer with air and ground with an impact grinder (a Fitz mill with 50 mesh screen) to obtain 30.9 kg of a

phosphate-binding polymer particles. (true specific gravity: 1.2530)

[Lot (d)]

To a reaction kettle, were added a 50% poly(allylamine hydrochloride) aqueous solution (280 kg), which corresponds to 140 kg of poly(allylamine hydrochloride), and water (420 kg). The mixture was stirred and the pH was adjusted to 10 with NaOH and acetonitrile (666 kg) was added to the mixture and stirred. Wile stirring the solution, epichlorohydrin (13.2 kg) was added and the mixture was stirred until it gelled. The resulting gel was allowed to continued curing for 21 hours at room temperature and the solvent was removed by filtration. The resulting gel was rinsed with water and 70% isopropanol and the solvent was removed. The rinsing was repeated until the electric conductivity of the filtrate reached at less than .010 mS/cm. Then, the gel was dried in a vacuum dryer and ground with an impact grinder (a hummer mill with 50 mesh screen) to obtain 63 kg of a phosphate-binding polymer particles. (true specific gravity: 1.2094)

[Lot (i)]

To a reaction kettle, were added a 51% poly(allylamine hydrochloride) aqueous solution (177.3 kg), which corresponds to 90.4 kg of poly(allylamine hydrochloride), and water (219 kg). The mixture was stirred and the pH was

adjusted to 10 with NaOH and then water (24.6 kg) and acetonitrile (433.9 kg) was added to the mixture and stirred. Wile stirring the solution, epichlorohydrin (8.6 kg) was added and the mixture was stirred until it gelled. The resulting gel was allowed to continued curing for 21 hours at room temperature and the solvent was removed by filtration with a belt filter. The rinsing was repeated by adding water to the belt filter until the electric conductivity of the filtrate reached at less than 0.02 mS/cm. Then, the gel was separated by the belt filter and isopropanol was added to the gel. The mixture was stirred and the solvent was removed with a centrifugal separator (1000 rpm). After dried in a vacuum dryer, the gel was ground with an impact grinder (a Fitz mill with 50 mesh screen) to obtain 59.7 kg of a phosphate-binding polymer particles. (true specific gravity: 1.2084)

As is clear from the data in Table II, polymer particles prepared by the method of "Preparation 2" in the present application or by the method of Holmes always had a true specific gravity of more than 1.25. On the other hand, polymer particles prepared by the method of "Preparation 1" had a true specific gravity of 1.20 to 1.22.

2. Hardness and Maximum Weight Loss of uncoated tablets obtained from polymer particles prepared by "Preparation 1" or "Preparation 2":

(a) Polymer particles are compressed under a static pressure of 1750 kg into tablets of 10 mmϕ each weighing 300 mg as shown in Example 1 of the present application. The tablets obtained from polymer particles having a true specific gravity of 1.253 and prepared by Holmes (or Preparation 2) showed 3.6 KP and 5.6 KP. Incidentally, a compression pressure of around 2,000 kg for preparing tablets is almost the acceptable upper limit to a tableting machine. If the machine is continuously used at a compression pressure over the limit, it will cause fatigue failure of punches of the tableting machine.

On the other hand, the polymer particles of the present invention having a true specific gravity of from 1.209, 1.211 and 1.211, respectively provide tablets having a hardness of 23.9 KP, 24.3 KP and 15.5 KP, respectively. Please refer to Table 1 on page 13 of the specification of the present application.

(b) According to the similar method of Example 3, tablets containing the polymer particles were prepared with a tableting machine at a compression pressure of 2000 kg or 900 kg. The polymer particles had a true specific gravity of 1.21 and a water content of 5.1 %. Tablets prepared had a weight of 290 mg/tablet, a diameter of 9.5 mmϕ and contained 250 mg of the polymer particles per tablet on a

dry basis.

The thus prepared tablets were subjected to a test for measuring a maximum weight loss according to The United States Pharmacopeia (USP) 24, The National Formulary (NF) 19, No. 1216-Tablet Friability. The test were conducted at 25 rpm for 30 minutes.

The test results are shown in the following Table Ⅲ. The results are an average of 20 tablets.

Table Ⅲ:

Lot	Compression Pressure (kg)	Hardness (KP)	Weight Loss (%)
F-1	2,000	16.7	0.85
F-1B	900	5.0	4.23

As is clear from the test results in Table Ⅲ, the tablet having a hardness of 5 KP showed a weight loss of 4.23% which is not deemed to be desirable for coating process. While the tablet having a hardness of 16.7 KP which is deemed to be desirable for coating.

When the uncoated tablets shown in Table Ⅲ were subjected to film coating, a tablet having a hardness of 5 KP indicated a remarkable weight loss on its surface at the beginning stage of the coating step thereby producing a significantly rough surface of the coated tablet. On the other hand, the tablet having a hardness of 16.7 KP produced the coated tablet having a smooth surface.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated this 10 th day of November, 2003

By: Katsuya Matsuda

Katsuya Matsuda